

Role of glutamic acid decarboxylase in the prepubertal inhibition of the luteinizing hormone releasing hormone release in female rhesus monkeys.

Mitsushima D; Marzban F; Luchansky L L; Burich A J; Keen K L; Durning M; Golos T G; Terasawa E

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Journal of neuroscience : the official journal of the Society for Neuroscience (UNITED STATES) Apr 15 1996, 16 (8) p2563-73, ISSN 0270-6474 Journal Code: 8102140

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Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

To investigate further the role of GABA in the onset of puberty, this study examines whether glutamic acid decarboxylase (GAD), the catalytic enzyme for GABA synthesis, is involved in the suppression of luteinizing hormone releasing hormone (LHRH) before puberty in rhesus monkeys. First, both GAD67 and GAD65 mRNAs were detectable by reverse transcription-PCR analysis in the preoptic area, medio-basal hypothalamus, posterior hypothalamic area, and hippocampus of the monkey brain. Second, effects of antisense oligodeoxynucleotides (D-oligos) for GAD67 and GAD65 mRNAs on LHRH release were examined in conscious female rhesus monkeys at the prepubertal stage using a push-pull perfusion method. The GAD67 or GAD65 antisense D-oligos or scrambled D-oligos were infused directly into the stalk-median eminence. Both the GAD67 and the GAD65 antisense D-oligos induced a large and prompt increase in LHRH release, whereas the scrambled D-oligos did not induce any significant effect. The results suggest that the removal of GABA inhibition by interfering with GAD synthesis is effective in increasing LHRH release in prepubertal monkeys. Third, the specificity of the antisense D-oligos on GAD levels was examined by incubating basal hypothalami with D-oligos in vitro and subsequent Western blot analysis. The antisense D-oligos consistently decreased the proteins GAD67 and GAD65 compared with respective control D-oligos. We conclude that the decrease of tonic GABAergic inhibition and maturational changes in GAD synthesis may be critical factors for the onset of puberty in nonhuman primates.

2/3,AB/19 (Item 19 from file: 155)  
DIALOG(R) File 155:MEDLINE(R)

08720655 96066731 PMID: 7472460

Differential expression of AMPA receptor subunits in NOS-positive neurons of cortex, striatum, and hippocampus.

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Journal of neuroscience : the official journal of the Society for Neuroscience (UNITED STATES) Nov 1995, 15 (11) p7046-61, ISSN 0270-6474 Journal Code: 8102140

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

AMPA receptor (AMPA) subunits expression was studied in nitric oxide synthase (NOS)-positive neurons of the adult rat cortex, striatum, and hippocampus, by a double-labeling approach, combining nonradioactive in situ hybridization and immunocytochemistry. The majority of cortical and hippocampal NOS-immunopositive neurons were characterized by a predominant expression of GluR-A and -D mRNA and low or undetectable expression of GluR-B and -C mRNA. In the striatum, the expression profile of AMPAR subunits in NOS-positive neurons differed from that in the other two

192 = Rat  
304 = human  
67 = Saimiri  
SCIENCE monkey

regulation of GAD67 gene expression in the GPI may be critical to the expression of parkinsonian motor signs and suggest a potential new treatment strategy for Parkinson's disease.

2000

2/3,AB/33 (Item 3 from file: 5)  
DIALOG(R)File 5:Biosis Previews(R)  
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12291150 BIOSIS NO.: 200000049017  
Autoimmune diabetes: Is **GAD** the culprit?  
AUTHOR: Lopez-Liuchi Jose V(a)  
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de Medecine Interne, Hopital Universitaire de Geneve, Rue  
Micheli-du-Crest 24, 1211, Geneva 14\*\*Switzerland  
JOURNAL: European Journal of Endocrinology 141 (5):p458-459 Nov., 1999  
ISSN: 0804-4643  
DOCUMENT TYPE: Article  
RECORD TYPE: Citation  
LANGUAGE: English  
1999

2/3,AB/34 (Item 4 from file: 5)  
DIALOG(R)File 5:Biosis Previews(R)  
(c) 2002 BIOSIS. All rts. reserv.

10074455 BIOSIS NO.: 199598529373  
**Antisense** oligonucleotide modulation of **GAD** alters  
cocaine-induced seizures in mice.  
AUTHOR: Abel M S; Kirages T J  
AUTHOR ADDRESS: Dep. Cell Biol. Anatomy, FUHS/Chicago Medical School,  
Chicago, IL 60064\*\*USA  
JOURNAL: Society for Neuroscience Abstracts 21 (1-3):p1592 1995  
CONFERENCE/MEETING: 25th Annual Meeting of the Society for Neuroscience  
San Diego, California, USA November 11-16, 1995  
ISSN: 0190-5295  
RECORD TYPE: Citation  
LANGUAGE: English  
1995

2/3,AB/35 (Item 5 from file: 5)  
DIALOG(R)File 5:Biosis Previews(R)  
(c) 2002 BIOSIS. All rts. reserv.

08080290 BIOSIS NO.: 000042084413  
INTRACEREBRAL ADMINISTRATION OF GLUTAMIC ACID DECARBOXYLASE **GAD**  
**ANTISENSE** OLIGODEOXYNUCLEOTIDE REDUCES LORDOSIS BEHAVIOR IN THE RAT  
AUTHOR: MCCARTHY M M; SCHWARTZ-GIBLIN S; PFAFF D W  
AUTHOR ADDRESS: ROCKEFELLER UNIV., NEW YORK, N.Y. 10021.  
JOURNAL: 21ST ANNUAL MEETING OF THE SOCIETY FOR NEUROSCIENCE, NEW ORLEANS,  
LOUISIANA, USA, NOVEMBER 10-15, 1991. SOC NEUROSCI ABSTR 17 (1-2). 1991.  
497. 1991  
CODEN: ASNEE  
DOCUMENT TYPE: Meeting  
RECORD TYPE: Citation  
LANGUAGE: ENGLISH  
1991

2/3,AB/36 (Item 6 from file: 5)

together, the present results suggest that **GAD** may play an important role in the onset and progress of puberty in nonhuman primates.

2/3,AB/15 (Item 15 from file: 155)  
DIALOG(R) File 155:MEDLINE(R)

09883853 98324116 PMID: 9659931

Gastrulation initiation in *Caenorhabditis elegans* requires the function of **gad-1**, which encodes a protein with WD repeats.

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Developmental biology (UNITED STATES) Jun 15 1998, 198 (2) p253-65, ISSN 0012-1606 Journal Code: 0372762

Contract/Grant No.: HD-11762; HD; NICHD; HD-29397; HD; NICHD

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Gastrulation in *Caenorhabditis elegans* is normally initiated by inward migration of the two gut precursor (E) cells at the 26-cell stage. A strong loss-of-function, temperature-sensitive, embryonic lethal mutation in the maternally required gene **gad-1** (gastrulation defective) prevents gastrulation initiation. In embryos from homozygous mutant **gad-1** (ct226) hermaphrodites reared at 25 degrees C, the E cells divide early with abnormal spindle orientations and fail to migrate into the embryo, and no subsequent gastrulation movements occur. These embryos continue to develop and differentiate the major cell types, but they undergo little morphogenesis. The temperature-sensitive period of the mutant is during early embryogenesis, prior to gastrulation onset. The predicted translation product of the cloned **gad-1** gene includes six beta-transducin-related repeats of the WD motif, which has been implicated in protein-protein interactions. The ct226 mutation alters a conserved residue in one of these repeats. Injection of **gad-1 antisense** RNA into wild-type hermaphrodites mimics the mutant phenotype in progeny embryos. We conclude that the **gad-1** gene product is required for initiation of gastrulation in *C. elegans*.

2/3,AB/16 (Item 16 from file: 155)  
DIALOG(R) File 155:MEDLINE(R)

09749691 98186690 PMID: 9518663

Effect of injection of **antisense** oligodeoxynucleotides of **GAD** isozymes into rat ventromedial hypothalamus on food intake and locomotor activity.

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Brain research (NETHERLANDS) Feb 16 1998, 784 (1-2) p305-15, ISSN 0006-8993 Journal Code: 0045503

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

In the ventromedial hypothalamus (VMH), gamma-aminobutyric acid (GABA) plays a role in regulating feeding and running behaviors. The GABA synthetic enzyme, glutamic acid decarboxylase (**GAD**), consists of two isozymes, GAD65 and GAD67. In the present study, the phosphorothioated **antisense** oligodeoxynucleotides (ODNs) of each **GAD** isozyme were injected bilaterally into the VMH of male rats, and food intake, body weight and locomotor activity were monitored. ODNs were incorporated in the water-absorbent polymer (WAP, 0.2 nmol/microliter) so that ODNs were

retained at the injection site. Each **antisense** ODN of GAD65 or GAD67 tended to reduce food intake on day 1 (day of injection=day 0) though not significantly. An injection combining both **antisense** ODNs significantly decreased food intake only on day 1, but body weight remained significantly lower than the control for 5 days. This suppression of body weight gain could be attributed to a significant increase in locomotor activity between days 3 and 5. Individual treatment with either ODNs did not change locomotor activity. The increase in daily locomotor activity in the group receiving the combined **antisense** ODNs occurred mainly during the light phase. Neither vehicle (WAP) nor control ODN affected food intake, body weight and locomotor activity. Histological studies indicated that **antisense** ODN distributed within 800 micron from the edge of the area where WAP was located 24 h after the injection gradually disappeared within days, but still remained within 300 micron m distance even 7 days after the injection. **Antisense** ODN was effectively incorporated by all the cell types examined, i.e., neurons, astrocytes and microglia. Further, HPLC analysis revealed that **antisense** ODNs of **GAD** isozymes, either alone or combined, decreased the content of GABA by 50% in VMH 24 h after the injection. These results indicate that suppression of GABA synthesis by either of the **GAD** isozymes is synergistically involved in suppressing food intake and enhancing locomotor activity in rat VMH. Copyright 1998 Elsevier Science B.V.

2/3,AB/17 (Item 17 from file: 155)  
DIALOG(R) File 155:MEDLINE(R)

09670383 98075846 PMID: 9383335

**Antisense** inhibition of R-cognin expression modulates differentiation of retinal neurons in vitro.

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Department of Biology, Boston University, Boston, MA 02215, USA.

Molecular vision computer file (UNITED STATES) Nov 21 1997, 3 p12,  
ISSN 1090-0535 Journal Code: 9605351

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

PURPOSE: Retina cognin (R-cognin) is a 50 kDa membrane-associated polypeptide expressed during retinogenesis where it is involved in mediating tissue-specific cell-cell interactions. In addition to its intercellular role in aggregation, R-cognin may act as a cell surface signaling molecule. An **antisense** oligonucleotide was used to inhibit R-cognin expression and to investigate the effects of this inhibition on subsequent neuronal differentiation. METHODS: Cultures of retina cells were prepared from 6 day (E6) and 8 day (E8) chicken embryos and were incubated with a deoxyoligonucleotide complementary to 20 bases of the sequence encoding R-cognin or random oligonucleotides. The levels of choline acetyltransferase (ChAT) and glutamic acid decarboxylase (**GAD**), markers of cholinergic and GABAergic differentiation, respectively, were detected by Western blots on protein extracts from treated cultures. RESULTS: The **antisense** treatment inhibited ChAT levels at E6 and **GAD** levels at E8. The treatment resulted in no decrease in the level of the enzyme glyceraldehyde 3-phosphate dehydrogenase. A random oligonucleotide did not affect the levels of any of the proteins. CONCLUSIONS: These results confirm the cell recognition role of R-cognin and suggest that it is important in intracellular signaling cascades necessary for normal retina development.

2/3,AB/18 (Item 18 from file: 155)  
DIALOG(R) File 155:MEDLINE(R)

08915179 96256692 PMID: 8786432

regions. This is reflected in the overall low expression of all AMPA receptor subunits and the paucity of GluR-D subunit expression that contrasts with the high expression of this subunit in NOS-positive cells in the hippocampus. Double-labeling experiments revealed a substantial correspondence between mRNA and protein levels of AMPAR subunits. Further evidence for the regional diversity of NOS-positive neurons is derived from the expression analysis of glutamate decarboxylase (GAD)-65 and -67 mRNAs. NOS-positive neurons expressed high levels of GAD-65, but not -67 in the cortex, high levels of both forms in the hippocampus, and low or undetectable levels of both mRNAs in the striatum. Despite of these differences, NOS-positive neurons share the common feature of low GluR-B subunit expression, suggesting the presence of AMPAR channels with high Ca<sup>2+</sup> permeability, regardless of the regional location. The relative resistance of NOS-positive interneurons in neurodegenerative diseases suggests that glutamate receptor-mediated Ca<sup>2+</sup> influx alone does not suffice to explain neuronal vulnerability, and additional factors have thus to be considered.

2/3,AB/20 (Item 20 from file: 155)  
DIALOG(R)File 155:MEDLINE(R)

08391251 95157170 PMID: 7854044

Expression of GAD mRNA in spinal cord neurons of normal and monoarthritic rats.

Castro-Lopes J M; Tolle T R; Pan B; Zieglgansberger W  
Institute of Histology and Embryology, Faculty of Medicine of Oporto, Porto, Portugal.

Brain research. Molecular brain research (NETHERLANDS) Oct 1994, 26 (1-2) p169-76, ISSN 0169-328X Journal Code: 8908640

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

This study was carried out to investigate whether the increase of GABA levels in spinal cord dorsal horn in response to chronic inflammatory lesions results from an enhanced expression of the gene that governs the production of glutamate decarboxylase (GAD), the enzyme responsible for GABA synthesis. In situ hybridization was used to visualize neurons expressing GAD mRNA within the spinal cord, in both intact rats and in animals bearing chronic monoarthritis induced by intraarticular injection of complete Freund's adjuvant. In control normal animals, neuronal labeling by an antisense oligonucleotide probe occurred throughout the spinal gray matter, except in the motoneuronal pool of Rexed's lamina IX. In treated animals 4 days after the induction of monoarthritis, a significant increase in the number of labeled cells occurred in the superficial laminae (25.3%) and the neck (17.2%) of the ipsilateral dorsal horn at segments L4-L5 which contain the projection domain of the ankle joint. At 2 weeks, values were, respectively, 20.2% and 13.9% over contralateral values, and an increase of 12.4% was found in the ventral horn. At 3 weeks, the ipsilateral increase of labeled cells was restricted to the superficial dorsal horn (15.2%). These findings emphasize the role played by the spinal GABAergic system in the modulation of chronic nociceptive input. It is suggested that the response of the spinal GABAergic system depends on the activation of GAD gene transcription in spinal neurons.

2/3,AB/21 (Item 21 from file: 155)  
DIALOG(R)File 155:MEDLINE(R)

08164450 94297781 PMID: 8025712

Distribution of glutamatergic receptors and GAD mRNA-containing neurons in the vestibular nuclei of normal and hemilabyrinthectomized rats.

de Waele C; Abitbol M; Chat M; Menini C; Mallet J; Vidal P P  
Laboratoire de Physiologie de la Perception et de l'Action, CNRS-College  
de France, Paris.

European journal of neuroscience (ENGLAND) Apr 1 1994, 6 (4) p565-76  
, ISSN 0953-816X Journal Code: 8918110

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Vestibular compensation is an attractive model for investigations of cellular mechanisms underlying post-lesional plasticity in the adult central nervous system. Immediately after hemilabyrinthectomy, the spontaneous activity in the deafferented second-order vestibular neurons falls to zero, resulting in a strong asymmetry between the resting discharge of the vestibular complexes on the lesioned and intact sides. This asymmetry most probably causes the static and dynamic vestibular deficits observed in the acute stage. After approximately 50 h, the deafferented vestibular neurons recover a quasi-normal resting activity which is thought to be the key of the compensation of the static vestibular syndromes. However, the molecular mechanisms underlying this recovery are unknown. In this study, we investigate possible changes in the distribution of glutamatergic N-methyl-D-aspartate (NMDA) and glutamate metabotropic receptors and of glutamate decarboxylase 67k (**GAD 67k**) mRNAs in the deafferented vestibular neurons induced by the labyrinthine lesion. Specific radioactive oligonucleotides were used to probe sections of rat vestibular nuclei according to in situ hybridization methods. Animals were killed at different times (5 h, 3 days and 3 weeks) following the lesion. Signal was detected by means of film or emulsion autoradiography. In the normal animals, several brainstem regions including the medial, lateral, inferior and superior vestibular nuclei were densely labelled by the **antisense** oligonucleotide NMDAR1 probe. However, the vestibular nuclei were not labelled by the glutamate metabotropic oligonucleotide **antisense** probe (mGluR 1). The **GAD 67k antisense** oligonucleotide probe labelled numerous small- to medium-sized central vestibular neurons but not the larger cell bodies in the lateral vestibular nucleus. This agrees with previous studies. In the hemilabyrinthectomized rats, no asymmetry could be detected, at either the autoradiographic or cellular levels, between the two medial vestibular nuclei whatever the probe used and whatever the delay following the lesion. However, for the NMDAR1 probe, the mean density of silver grains in both the deafferented and intact medial vestibular neurons was 20% lower 5 h after the lesion. Three days and 3 weeks later, the intensity of labelling over all cells was the same as in the control group. Further studies are necessary to confirm the relatively weak modification of the NMDAR1 mRNAs expression and to exclude a change of **GAD 65** and of other NMDA subunit mRNAs during the vestibular compensation process.

2/3,AB/22 (Item 22 from file: 155)  
DIALOG(R)File 155:MEDLINE(R)

08146942 94282571 PMID: 8012804

Intracerebral administration of **antisense** oligodeoxynucleotides to **GAD65** and **GAD67** mRNAs modulate reproductive behavior in the female rat.

McCarthy M M; Masters D B; Rimvall K; Schwartz-Giblin S; Pfaff D W  
Rockefeller University, Laboratory of Neurobiology and Behavior, New  
York, NY 10028.

Brain research (NETHERLANDS) Feb 14 1994, 636 (2) p209-20, ISSN  
0006-8993 Journal Code: 0045503

Contract/Grant No.: HD-05751; HD; NICHD

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Increased GABA activity in the medial hypothalamus (HYP) and midbrain central gray (MCG), but not the preoptic area (POA), facilitates sexual receptivity in the female rat [40]. In the current experiments, ovariectomized females were chronically treated with estrogen (via silastic capsules) to maintain a continuously high level of lordosis response. Administration of crystalline **antisense** oligodeoxynucleotide to the GABA synthetic enzyme, GAD67, into the HYP and MCG significantly and reversibly reduced lordosis response for 1-2 days, but did not inhibit lordosis when administered into the POA. Administration of a control oligonucleotide, consisting of the same nucleotide bases but in a scrambled sequence, did not significantly modulate behavior when infused into any brain areas. When oligodeoxynucleotide **antisense** to GAD67 was suspended in oil and then infused into the HYP or MCG it was more effective and resulted in less inter-animal variability. Subsequent experiments involving infusions into the MCG compared the effectiveness of **antisense** oligonucleotides to the two different forms of GAD, known as GAD65 and GAD67. Oligodeoxynucleotides **antisense** to the mRNA for either gene were effective at reducing lordosis behavior but with a different time course. Oligonucleotide **antisense** to GAD67 significantly reduced behavior within 24 h of infusion and there was full recovery by 4 days post-infusion. GAD65 **antisense** oligonucleotide did not significantly reduce behavior until 48 h post infusion and animals did not fully recover to pretest levels of lordosis until 5 days post-infusion. When **antisense** oligonucleotide for the two genes was administered simultaneously, the inhibition of lordosis was maximal at 24 h and stayed depressed for 4 days. There did not appear to be an additive effect of the two different **antisense** oligonucleotides when administered together. Tissue GABA levels in HYP and MCG of individual rats assayed by HPLC were no longer correlated with lordosis score after **antisense** oligonucleotide infusion but were after infusions of scrambled control oligos. Immunoblotting for the two forms of GAD revealed that GAD67 **antisense** oligonucleotide infusion led to significant decreases in both GAD67 and GAD65 protein levels as compared to infusions of scrambled control oligo. In addition, the levels of a neuronal marker, neuron-specific enolase, also decreased (although nonsignificantly) suggesting either a temporary shutdown of protein synthesis or a degeneration of GABAergic neurons after GAD67 **antisense** oligonucleotide infusion.

2/3,AB/23 (Item 23 from file: 155)  
DIALOG(R)File 155:MEDLINE(R)

08093683 94235976 PMID: 8180490

Activity-dependent changes in GAD and preprotachykinin mRNAs in visual cortex of adult monkeys.

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Department of Anatomy and Neurobiology, University of California at Irvine 92717.

Cerebral cortex (New York, N.Y. : 1991) (UNITED STATES) Jan-Feb 1994,

4 (1) p40-51, ISSN 1047-3211 Journal Code: 9110718

Contract/Grant No.: EY07193; EY; NEI; NS21377; NS; NINDS

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Tachykinin-immunoreactive neurons are a subgroup of the GABA neuronal population in layer IVC of monkey primary visual cortex. Following brief periods of monocular deprivation in adult monkeys, immunoreactivity for both GABA and tachykinins is dramatically reduced in layer IV cells that lie within the deprived ocular dominance columns of this cortical area. The present study shows that these activity-dependent changes are associated with changes in mRNA levels but over different time courses. Radioactive **antisense** riboprobes derived from monkey-specific cDNAs were used to

localize glutamic acid decarboxylase (GAD) and beta-preprotachykinin (beta PPT) mRNAs by in situ hybridization histochemistry. GAD and beta PPT mRNAs decreased in deprived ocular dominance columns of adult monkeys when neural activity was abolished in one eye by intraocular injections of tetrodotoxin (TTX). beta PPT mRNA levels fell within 5 d of deprivation and thus appeared to parallel the fall in immunodetectable tachykinin levels. By contrast, reduced GAD mRNA levels were detectable only after 15 d of deprivation and long after the fall in immunoreactive GAD and GABA levels has maximized. These results suggest that tachykinin gene expression is regulated by transcriptional mechanisms as part of the first response to reduced neural activity whereas the initial downregulation of immunoreactive GAD and GABA depends on posttranscriptional mechanisms. Following a more prolonged period of deprivation, a secondary mechanism for GAD regulation appears to be engaged at the level of gene transcription or possibly by changes in mRNA stability.

2/3,AB/24 (Item 24 from file: 155)  
DIALOG(R) File 155:MEDLINE(R)

07999985 94133894 PMID: 8302162

Glutamic acid decarboxylase gene expression in thalamic reticular neurons transplanted as a cell suspension in the adult thalamus.

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INSERM CJF 91-02, Faculte de Medecine, Creteil, France.

Brain research. Molecular brain research (NETHERLANDS) Nov 1993, 20

(3) p245-53, ISSN 0169-328X Journal Code: 8908640

Contract/Grant No.: NS29230; NS; NINDS

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

The goal of the present study was to determine whether alterations in neuronal morphology and connections in thalamic grafts were accompanied by changes in the expression of mRNA encoding glutamic acid decarboxylase (GAD), the key enzyme in the synthesis of GABA, the normal neurotransmitter of neurons of the thalamic reticular nucleus. Cell suspensions of rat fetal tissue containing both thalamic reticular nucleus and ventrobasal primordia were transplanted into the excitotoxically lesioned somatosensory thalamus of adult rats. Levels of messenger RNA (mRNA) encoding GAD (Mr 67,000; GAD67) were measured 7 days to 4 months following transplantation via quantitative in situ hybridization with 35S-radiolabeled antisense RNAs. Expression of GAD67 mRNA in the thalamic reticular nucleus was analyzed in parallel in rat pups between 0 and 30 days postnatally, and in adult animals. As already observed with immunohistochemistry, transplanted neurons of the thalamic reticular nucleus did not group in specific clusters but rather mingled with unlabeled (putatively ventrobasal) neurons. Levels of labelling for GAD67 mRNA per neuron increased over time and reached adult levels during the third week post-grafting, i.e. 2 weeks after the theoretical birthdate of the neurons (grafted at embryonic days 15-16). Similar values were observed and a plateau was reached at similar time points during normal ontogeny. The results suggest that, in contrast to morphology and size of the neuronal cell bodies, gene expression of GAD67 develops normally despite the ectopic location of neurons of the thalamic reticular nucleus in the somatosensory thalamus, the abnormal connectivity and the lack of segregation from non-GABAergic neurons. (ABSTRACT TRUNCATED AT 250 WORDS)

2/3,AB/25 (Item 25 from file: 155)  
DIALOG(R) File 155:MEDLINE(R)

07469443 92408434 PMID: 1326694



Expression of glutamic acid decarboxylase messenger RNA in rat medial preoptic area neurones during the oestrous cycle and after ovariectomy.

Herbison A E; Augood S J; McGowan E M

Department of Neuroendocrinology, AFRC Institute of Animal Physiology and Genetics Research, Babraham, Cambridge, UK.

Brain research. Molecular brain research (NETHERLANDS) Aug 1992, 14

(4) p310-6, ISSN 0169-328X Journal Code: 8908640

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Evidence suggests that medial preoptic area (MPOA) neurones containing gamma-aminobutyric acid (GABA) are modulated directly by oestrogen. We have used an alkaline phosphatase-labelled **antisense** oligonucleotide probe to examine glutamic acid decarboxylase67 (**GAD**) mRNA expression within individual cells of the MPOA, diagonal band of Broca (DBB) and parietal cortex in rats killed at noon on each day of the oestrous cycle and after ovariectomy (n = 4-5). As a fall in extracellular GABA concentrations occurs in the MPOA on the afternoon of proestrus, the GAD67 mRNA content of cells was also examined in proestrous rats at 15:00h immediately prior to the preovulatory luteinising hormone (LH) surge. The MPOA was found to have an intermediate number of GAD67 mRNA-containing cells compared with the DBB and cortex (P less than 0.01) but expressed the lowest mean hybridisation signal (P less than 0.01). The parietal cortex had significantly fewer (P less than 0.01) **GAD** mRNA-containing cells than either the MPOA or DBB but these contained higher mean density of signal (P less than 0.01). The hybridisation signal for **GAD** mRNA was abolished by either ribonuclease pre-treatment or the use of excess non-labelled probe. No significant (P greater than 0.05) differences in GAD67 mRNA were detected in animals killed at noon throughout the oestrous cycle or after ovariectomy. On the afternoon of proestrus (15:00h) there was a significant 40% reduction in mean GAD67 mRNA content within cells of only the MPOA compared with noon (P less than 0.05). The numbers of cells in the MPOA expressing GAD67 mRNA were not significantly different. (ABSTRACT TRUNCATED AT 250 WORDS)

2/3,AB/26 (Item 26 from file: 155)  
DIALOG(R) File 155:MEDLINE(R)

07144125 92076443 PMID: 1660350

Cellular distribution of L-glutamate decarboxylase (**GAD**) and gamma-aminobutyric acidA (GABAA) receptor mRNAs in the retina.

Brecha N C; Sternini C; Humphrey M F

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Cellular and molecular neurobiology (UNITED STATES) Oct 1991, 11 (5)  
p497-509, ISSN 0272-4340 Journal Code: 8200709

Contract/Grant No.: DK 38752; DK; NIDDK; DK 40469; DK; NIDDK; EY 04067;  
EY; NEI

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

1. Gamma-aminobutyric acid (GABA), a major inhibitory transmitter of the vertebrate retina, is synthesized from glutamate by L-glutamate decarboxylase (**GAD**) and mediates neuronal inhibition at GABAA receptors. **GAD** consists of two distinct molecular forms, GAD65 and GAD67, which have similar distribution patterns in the nervous system (Feldblum et al., 1990; Erlander and Tobin, 1991). GABAA receptors are composed of several distinct polypeptide subunits, of which the GABAA alpha 1 variant has a particularly extensive and widespread distribution in the nervous system. The aim of this study was to determine the cellular localization patterns of **GAD** and GABAA alpha 1 receptor mRNAs to define GABA- and GABAA receptor-synthesizing neurons in the rat retina. 2.

GAD and GABAA alpha 1 mRNAs were localized in retinal neurons by in situ hybridization histochemistry with 35S-labeled antisense RNA probes complementary to GAD67 and GABAA alpha 1 mRNAs. 3. The majority of neurons expressing GAD67 mRNA is located in the proximal inner nuclear layer (INL) and ganglion cell layer (GCL). Occasional GAD67 mRNA-containing neurons are present in the inner plexiform layer. Labeled neurons are not found in the distal INL or in the outer nuclear layer (ONL). 4. GABAA alpha 1 mRNA is expressed by neurons distributed to all regions of the INL. Some discretely labeled cells are present in the GCL. Labeled cells are not observed in the ONL. 5. The distribution of GAD67 mRNA demonstrates that numerous amacrine cells (conventional, interstitial, and displaced) and perhaps interplexiform cells synthesize GABA. These cells are likely to employ GABA as a neurotransmitter. 6. The distribution of GABAA alpha 1 mRNA indicates that bipolar, amacrine, and perhaps ganglion cells express GABAA receptors having an alpha 1 polypeptide subunit, suggesting that GABA acts directly upon these cells.

2/3,AB/27 (Item 27 from file: 155)  
DIALOG(R) File 155:MEDLINE(R)

06928825 91232384 PMID: 1709439

Calcium binding protein (calbindin-D28k) and glutamate decarboxylase gene expression after kindling induced seizures.

Sonnenberg J L; Frantz G D; Lee S; Heick A; Chu C; Tobin A J; Christakos S

Department of Biochemistry and Molecular Biology, UMDNJ-New Jersey Medical School, Newark 07103.

Brain research. Molecular brain research (NETHERLANDS) Feb 1991, 9 (3) p179-90, ISSN 0169-328X Journal Code: 8908640

Contract/Grant No.: NS20270; NS; NINDS; NS20356; NS; NINDS; NS22256; NS; NINDS

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

In order to determine whether calcium binding protein (calbindin-D28k or CaBP) and glutamate decarboxylase (GAD) may be involved in the process underlying the generation of seizure activity, changes in CaBP protein and mRNA and in GAD mRNA were examined in the kindling model of epilepsy. Following amygdaloid (AK) and commissure (CK) kindling significant decreases in the concentration of CaBP of 20% and 30%, respectively, were specifically observed in the hippocampal formation. However, using a cDNA specific to mammalian CaBP, Northern analysis of poly(A+) RNA and slot blot analysis of total RNA revealed no changes in the levels of CaBP mRNA in hippocampus, subcortical area (including amygdala, substantia nigra and striatum) or cerebellum of rats sacrificed 30 min, 1 h, 6 h or 24 h after the last kindled seizure. Similarly when these blots were reprobbed with a cDNA specific to mammalian GAD, no changes in GAD gene expression were observed. However, fos gene expression was markedly enhanced at 1 h after seizure. We also tested whether changes in CaBP or GAD mRNA could be detected at any of the various stages of the kindling process. Slot blot analysis of cortex, subcortical structures and hippocampus revealed no changes in CaBP or GAD mRNA during the course of commissure kindling. In situ hybridization studies with GAD and CaBP 35S-labeled antisense probes also indicated no obvious changes upon visual analysis of autoradiographs. However, when silver grains were counted, significant changes in GAD mRNA in individual cells in hippocampus and substantia nigra were noted after kindling induced epilepsy. Our results indicate that, unlike fos gene expression, prominent alterations in GAD and CaBP mRNA in gross brain regions (as measured by slot blot and Northern blot analyses) are not observed in the kindling process. However, our in situ hybridization studies suggest that changes in GAD mRNA in individual cells may be involved in the process

underlying kindling induced seizure activity.

2/3,AB/28 (Item 28 from file: 155)  
DIALOG(R)File 155:MEDLINE(R)

06800565 91093752 PMID: 1846011

Differential effects of monocular deprivation on glutamic acid decarboxylase and type II calcium-calmodulin-dependent protein kinase gene expression in the adult monkey visual cortex.

Benson D L; Isackson P J; Gall C M; Jones E G

Department of Anatomy and Neurobiology, University of California, Irvine 92717.

Journal of neuroscience : the official journal of the Society for Neuroscience (UNITED STATES) Jan 1991, 11 (1) p31-47, ISSN 0270-6474  
Journal Code: 8102140

Contract/Grant No.: EY-07193; EY; NEI; NS26748; NS; NINDS

Erratum in J Neurosci 1991 May;11(5) followi

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Increases in immunocytochemically detectable type II calcium-calmodulin-dependent protein kinase (CaM II kinase) and decreases in immunocytochemically detectable glutamic acid decarboxylase (GAD) are known to occur in the visual cortex of adult monkeys following brief periods of monocular visual deprivation. In the present study, GAD and CaM II kinase gene expression was investigated under these conditions. The polymerase chain reaction (PCR) was used to generate species-specific cDNA clones that were used to make antisense RNA probes. A second form of CaM II kinase alpha, CaM II kinase alpha-33, which contains an additional phosphorylation consensus sequence, was identified. In situ hybridization in normal visual cortex revealed a complex sublaminal organization of GAD-expressing cells within layers IVC and VI and a distribution of CaM II kinase alpha-expressing cells that was greatest in layers II, III, IVB, and VI. In situ hybridization in the cortex from animals that had been monocularly deprived revealed enhanced CaM II kinase mRNA levels in deprived-eye columns of layer IVC and, associated with the deprived eye, cytochrome oxidase-stained periodicities in other layers. In layer IV, the enhancement of labeling in deprived-eye stripes was, on average, 16% greater than in normal-eye stripes. By contrast, GAD, mRNA levels appeared unchanged in all layers, suggesting a posttranscriptional regulatory mechanism.

2/3,AB/29 (Item 29 from file: 155)  
DIALOG(R)File 155:MEDLINE(R)

06470810 90166559 PMID: 3272189

The abnormal cerebellar organization of Weaver and reeler mice does not affect the cellular distribution of three neuronal mRNAs.

Wuenschell C W; Tobin A J

Department of Biology, University of California, Los Angeles 90024.

Neuron (UNITED STATES) Nov 1988, 1 (9) p805-15, ISSN 0896-6273

Journal Code: 8809320

Contract/Grant No.: GM 7104; GM; NIGMS; NS 20356; NS; NINDS

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

We used in situ hybridization of 35S-labeled antisense RNAs to study the cellular distribution of three neuronal mRNAs. We compared the expression of these RNAs in cerebellar Purkinje neurons in wild-type (C57Bl-6J) mice and in two mutants (Weaver and reeler) known to have

abnormal cerebellar morphologies. In normal mice, **GAD** mRNA is present in four sets of neurons in the cerebellar cortex while calbindin mRNA is present only in Purkinje neurons. Proenkephalin mRNA is present in Golgi II neurons as well as in a set of neurons in the deep part of the molecular layer. Despite the dramatic differences in structural organization and inputs of Purkinje neurons in the cerebella of adult Weaver and reeler mice, the expression of these RNAs appears unchanged. These results support the hypothesis that Purkinje cell cytodifferentiation proceeds autonomously after its inception in early embryonic life.

2/3,AB/30 (Item 30 from file: 155)  
DIALOG(R)File 155:MEDLINE(R)

05681588 88108851 PMID: 2448011

Glutamic acid decarboxylase mRNA in rat brain: regional distribution and effects of intrastriatal kainic acid.

Kim Y S; Thomas J W; Tillakaratne N J; Montpied P; Suzdak P D; Banner C; Ginns E; Tobin A J; Paul S M

Section on Molecular Pharmacology, NIMH, Bethesda, MD 20892.

Brain research (NETHERLANDS) Dec 1987, 427 (1) p77-82, ISSN 0006-8993 Journal Code: 0045503

Contract/Grant No.: NS20356; NS; NINDS; NS22256; NS; NINDS

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Glutamic acid decarboxylase (**GAD**) mRNA was quantified in different regions of rat brain using an **antisense** RNA probe (ribo-probe) prepared from a cloned feline cDNA. In all brain regions studied a single band of **GAD** mRNA of approximately 3.7 kb was detected. The level of **GAD** mRNA was highest in the cerebellum, followed by the hypothalamus greater than thalamus greater than striatum greater than hippocampus greater than frontal cortex = parietal cortex greater than or equal to medulla = pons. Since **GAD** has been previously localized to intrinsic neurons of the striatum, we examined the effects of intrastriatal kainic acid administration on striatal **GAD** mRNA. The level of **GAD** mRNA in the kainic acid-lesioned striatum was reduced by 70-75% when compared to the contralateral (unlesioned) striatum. In contrast, the level of glutamine synthetase (an enzyme localized to glia) mRNA was increased approximately 290% in the kainic acid-lesioned striatum. There were no significant differences in **GAD** mRNA levels between the ipsilateral and contralateral cerebral cortices and hippocampi of rats injected with intrastriatal kainic acid.

2/3,AB/31 (Item 1 from file: 5)  
DIALOG(R)File 5:Biosis Previews(R)  
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13631307 BIOSIS NO.: 200200260128

Effects of **antisense** glutamic aciddecarboxylase oligodeoxynucleotide on epileptic rats induced by pentylenetetrazol.

AUTHOR: He Xiaohua(a); Wang Wei; Ruan Xuzhong; Li Wenxin(a); Zhang Liang

AUTHOR ADDRESS: (a)Department of Virology and Molecular Biology, School of Life Sciences, Wuhan University, Wuhan, 430070\*\*China

JOURNAL: Chinese Medical Journal (English Edition) 115 (3):p425-429 March, 2002

MEDIUM: print

ISSN: 0366-6999

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: Objective To investigate the effects of **antisense** glutamic acid decarboxylase (GAD67) oligodeoxynucleotide (ODN) on behavior, seizure threshold and EEG of hippocampus in the epileptic rats induced by pentylenetetrazol (PTZ). Methods A model of chronic epilepsy in rats was established by PTZ. The inhibition of GAD67 mRNA expression in hippocampus was selectively induced by **antisense** oligodeoxynucleotide of GAD67. The effect of **antisense** GAD67 ODN on behavior, seizure threshold and EEG recording of kindled rats was examined. Results **Antisense** GAD67 ODN could inhibit the expression of GAD67 mRNA and the concentration of GABA. It also could significantly shorten the latencies of seizure and increase the level of seizure and the frequency of epileptiform discharges. Conclusion The gene of GAD67 may be an anti-seizure gene, which might inhibit epileptiform discharge. The treatment of epilepsy by GAD67 gene will have a bright future.

2002

2/3,AB/32 (Item 2 from file: 5)  
DIALOG(R)File 5:Biosis Previews(R)  
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12874741 BIOSIS NO.: 200100081890

Distribution of GAD65/GAD67 mRNA in the pallidal complex in normal and parkinsonian monkeys relevance for the design of a novel gene-based therapy for parkinsonism.

AUTHOR: Wade T V(a); Schneider J S

AUTHOR ADDRESS: (a)Thomas Jefferson Univ., Philadelphia, PA\*\*USA

JOURNAL: Society for Neuroscience Abstracts 26 (1-2):pAbstract No-4786  
2000

MEDIUM: print

CONFERENCE/MEETING: 30th Annual Meeting of the Society of Neuroscience New Orleans, LA, USA November 04-09, 2000

SPONSOR: Society for Neuroscience

ISSN: 0190-5295

RECORD TYPE: Abstract

LANGUAGE: English

SUMMARY LANGUAGE: English

ABSTRACT: The two isoforms of glutamic acid decarboxylase (GAD65 and GAD67), the synthesizing enzymes for GABA, may have different functional roles in regulating basal ganglia output and may have different regional and cellular distributions. Since altered pallidal GABAergic activity may underlie motor deficits observed in parkinsonism, we have investigated the regional distribution and differential expression of GAD65 and GAD67 mRNA at 4 rostrocaudal levels throughout the pallidal complex in normal and parkinsonian squirrel monkeys. In normal animals, GAD65 mRNA was expressed similarly in both internal (GPI) and external (GPe) pallidal segments with no significant rostrocaudal differences in gene expression. GAD67 mRNA was expressed to a greater extent in the GPI than the GPe, with higher levels expressed caudally. In MPTP-treated parkinsonian monkeys, GAD67 mRNA expression was increased in both the GPI and GPe with much larger increases in the GPI especially at more caudal levels. Only minor increases in GAD65 gene expression were observed in the GPI and gene expression was decreased in the GPe at all rostrocaudal levels. Based on the anatomical distributions of GAD isoforms in the pallidum and the assumption that increased activity of GABAergic GPI neurons underlie the expression of parkinsonian signs, we performed targeted application of GAD65 and GAD67 **antisense** oligonucleotides to the GPI in an attempt to selectively decrease the abnormal GABAergic activity and to partially ameliorate parkinsonian signs. Infusion of GAD67 **antisense** into the GPI in 3 parkinsonian monkeys caused increased motor activity that was not observed after infusions of a missense sequence or GAD65 **antisense**. These results show that

DIALOG(R)File 5:Biosis Previews(R)  
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07521515 BIOSIS NO.: 000091084644

CALCIUM BINDING PROTEIN CALBINDIN-D-28K AND GLUTAMATE DECARBOXYLASE GENE  
EXPRESSION AFTER KINDLING INDUCED SEIZURES

AUTHOR: SONNENBERG J L; FRANTZ G D; LEE S; HEICK A; CHU C; TOBIN A J;  
CHRISTAKOS S

AUTHOR ADDRESS: UMDNJ-NEW JERSEY MED. SCH., DEP. BIOCHEM. MOLECULAR BIOL.,  
185 S. ORANGE AVE., NEWARK, N.J. 07103-2757, USA.

JOURNAL: MOL BRAIN RES 9 (3). 1990. 179-190. 1990

FULL JOURNAL NAME: Molecular Brain Research

CODEN: MBREE

RECORD TYPE: Abstract

LANGUAGE: ENGLISH

ABSTRACT: In order to determine whether calcium binding protein (calbindin-D28k or CaBP) and glutamate decarboxylase (GAD) may be involved in the process underlying the generation of seizure activity, changes in CaBP protein and mRNA and in GAD mRNA were examined in the kindling model of epilepsy. Following amygdaloid (AK) and commissure (CK) kindling significant decreases in the concentration of CaBP of 20% and 30%, respectively, were specifically observed in the hippocampal formation. However, using a cDNA specific to mammalian CaBP, Northern analysis of poly(A+) RNA and shot blot analysis of total RNA revealed no changes in the levels of CaBP mRNA in hippocampus, subcortical area (including amygdala, substantia nigra and striatum) or cerebellum of rats sacrificed 30 min, 1 h, 6 h or 24 h after the last kindled seizure. Similarly when these blots were reprobbed with a cDNA specific to mammalian GAD, no changes in GAD gene expressions were observed. However, fos gene expression was markedly enhanced at 1 h after seizure. We also tested whether changes in CaBP or GAD mRNA could be detected at any of the various stages of the kindling process. Slot blot analysis of cortex, subcortical structures and hippocampus revealed no changes in CaBP or GAD mRNA during the course of commissure kindling. In situ hybridization studies with GAD and CaBP 35S-labeled antisense probes also indicated no obvious changes upon visual analysis of autoradiographs. However, when silver grains were counted, significant changes in GAD mRNA in individual cells in hippocampus and substantia nigra were noted after kindling induced epilepsy. Our results indicated that, unlike fos gene expression, prominent alterations in GAD and CaBP mRNA in gross brain regions (as measured by slot blot and Northern blot analyses) are not observed in the kindling process. However, our in situ hybridization studies suggest that changes in GAD mRNA in individual cells may be involved in the process underlying kindling induced seizure activity.

1990

2/3,AB/37 (Item 1 from file: 444)  
DIALOG(R)File 444:New England Journal of Med.  
(c) 2002 Mass. Med. Soc. All rts. reserv.

00115420

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Brief Report: Short Stature Caused by a Mutant Growth Hormone (Original Articles)

Takahashi, Yutaka; Kaji, Hidesuke; Okimura, Yasuhiko; Goji, Katsumi;  
Abe, Hiromi; Chihara, Kazuo.  
The New England Journal of Medicine  
Feb 15, 1996; 334 (7),pp 432-436

LINE COUNT: 00331

WORD COUNT: 04578

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? b 155, 5, 444

14nov02 11:42:16 User242957 Session D540.2  
\$0.00 0.073 DialUnits File410  
\$0.00 Estimated cost File410  
\$0.03 TELNET  
\$0.03 Estimated cost this search  
\$0.03 Estimated total session cost 0.234 DialUnits

SYSTEM:OS - DIALOG OneSearch

File 155:MEDLINE(R) 1966-2002/Nov W2

\*File 155: For updating information please see Help News155. Alert feature enhanced with customized scheduling. See HELP ALERT.

File 5:Biosis Previews(R) 1969-2002/Nov W1

(c) 2002 BIOSIS

\*File 5: Alert feature enhanced for multiple files, duplicates removal, customized scheduling. See HELP ALERT.

File 444:New England Journal of Med. 1985-2002/Nov W2

(c) 2002 Mass. Med. Soc.

Set Items Description

? s gad and antisens?

6174 GAD

35954 ANTISENS?

S1 57 GAD AND ANTISENS?

? rd

...examined 50 records (50)

...completed examining records

S2 37 RD (unique items)

? s gad and ribozym?

6174 GAD

6199 RIBOZYM?

S3 0 GAD AND RIBOZYM?

? t s2/3,ab/all

2/3,AB/1 (Item 1 from file: 155)

DIALOG(R) File 155:MEDLINE(R)

13111065 21937853 PMID: 11940381

Effects of **antisense** glutamic acid decarboxylase oligodeoxynucleotide on epileptic rats induced by pentylenetetrazol.

He Xiaohua; Wang Wei; Ruan Xuzhong; Li Wenxin; Zhang Liang

Department of Virology and Molecular Biology, School of Life Sciences, Wuhan University, Wuhan 430070, China.

Chinese medical journal (China) Mar 2002, 115 (3) p425-9, ISSN 0366-6999 Journal Code: 7513795

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

OBJECTIVE: To investigate the effects of **antisense** glutamic acid decarboxylase (**GAD** (67)) oligodeoxynucleotide (ODN) on behavior, seizure threshold and EEG of hippocampus in the epileptic rats induced by pentylenetetrazol (PTZ). METHODS: A model of chronic epilepsy in rats was established by PTZ. The inhibition of **GAD**(67) mRNA expression in hippocampus was selectively induced by **antisense** oligodeoxynucleotide of **GAD**(67). The effect of **antisense GAD** (67) ODN on behavior, seizure threshold and EEG recording of kindled rats was examined. RESULTS: **Antisense GAD**(67) ODN could inhibit the expression of **GAD** (67) mRNA and the concentration of GABA. It also could significantly shorten the latencies of seizure and increase the level of seizure and the frequency of epileptiform discharges. CONCLUSION: The gene of **GAD** (67) may be an anti-seizure gene, which might inhibit

PRIORITY  
11/05/98



epileptiform discharge. The treatment of epilepsy by **GAD**(67) gene will have a bright future.

2/3,AB/2 (Item 2 from file: 155)  
DIALOG(R) File 155:MEDLINE(R)

12572014 21477223 PMID: 11592837

Repression of **GAD** autoantigen expression in pancreas beta-Cells by delivery of **antisense** plasmid/PEG-g-PLL complex.

Lee M; Han S O; Ko K S; Koh J J; Park J S; Yoon J W; Kim S W  
Center for Controlled Chemical Delivery, Department of Pharmaceutics and Pharmaceutical Chemistry, University of Utah, Salt Lake City, Utah 84112, USA. minhyung.lee@deans.pharm.utah.edu

Molecular therapy : the journal of the American Society of Gene Therapy (United States) Oct 2001, 4 (4) p339-46, ISSN 1525-0016

Journal Code: 100890581

Contract/Grant No.: DK51689; DK; NIDDK

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

It was previously reported that silencing of the expression of glutamic acid decarboxylase (**GAD**) in transgenic nonobese diabetic (NOD) mice completely protected islet beta-cells against development of diabetes. This suggests that the repression of **GAD** autoantigen by somatic gene delivery can prevent autoimmune destruction of pancreatic beta-cells. To repress **GAD** expression in islet beta-cells, we delivered an **antisense GAD** mRNA expression plasmid (pRIP-AS-**GAD**) using poly(ethylene glycol)-grafted poly-L-lysine (PEG-g-PLL) as a gene carrier. In a gel retardation assay, the pRIP-AS-**GAD**/PEG-g-PLL complex was completely retarded above a weight ratio of 1:1.5 (plasmid: PEG-g-PLL). PEG-g-PLL protected the plasmid DNA from DNase I for more than 60 minutes. In a reporter gene transfection assay, PEG-g-PLL showed the highest transfection efficiency at a weight ratio of 1:3. We also transfected pRIP-AS-**GAD**/PEG-g-PLL complex into a **GAD**-producing mouse insulinoma (MIN6) cell line. The **antisense** mRNA was expressed specifically in beta-cells and expression was dependent on glucose level. The repression of **GAD** after transfection of pRIP-AS-**GAD** was confirmed by immunoblot assay. In addition, in vivo expression of **antisense** RNA in pancreas was confirmed by RT-PCR after intravenous injection of the complex into mice. Therefore, our study revealed that the pRIP-AS-**GAD**/PEG-g-PLL system is applicable for the repression of **GAD** autoantigen expression.

2/3,AB/3 (Item 3 from file: 155)  
DIALOG(R) File 155:MEDLINE(R)

11189388 21210816 PMID: 11299322

Enhanced neuronal protection from oxidative stress by coculture with glutamic acid decarboxylase-expressing astrocytes.

Lamigeon C; Bellier J P; Sacchettoni S; Rujano M; Jacquemont B  
Laboratoires de Neuro-Virologie Moleculaire et de Neurobiologie Experimentale et Physiopathologie, INSERM U433, Faculte de Medecine RTH Laennec Lyon, France.

Journal of neurochemistry (United States) Apr 2001, 77 (2) p598-606, ISSN 0022-3042 Journal Code: 2985190R

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Astrocytes expressing glutamic acid decarboxylase **GAD**67 directed by the glial fibrillary acidic protein promoter were shown to provide enhanced

protection of PC12 cells from H<sub>2</sub>O<sub>2</sub> treatment and serum deprivation in the presence of glutamate. In addition, they protected non-differentiated, but not differentiated, embryonic rat cortical neurons from glutamate toxicity. Glutamic acid decarboxylase (GAD)-expressing astrocytes showed increased glutathione synthesis and release compared to control astrocytes. These changes were due to GAD transgene expression, as transient expression of a GAD antisense plasmid resulted in partial suppression of the increase in glutathione release. In addition to the previously demonstrated increases in NADH and ATP levels and lactate release, GAD-expressing astrocytes show increased antioxidant activity, explaining their ability to protect neurons from various injuries.

2/3,AB/4 (Item 4 from file: 155)  
DIALOG(R) File 155:MEDLINE(R)

10978684 20536056 PMID: 11085606

Decreasing GAD neonatally attenuates steroid-induced sexual differentiation of the rat brain.

Davis A M; Grattan D R; McCarthy M M  
Department of Physiology, University of Maryland School of Medicine,  
Baltimore 21201, USA.

Behavioral neuroscience (UNITED STATES) Oct 2000, 114 (5) p923-33,  
ISSN 0735-7044 Journal Code: 8302411

Contract/Grant No.: MH52716; MH; NIMH

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

During development, exposure to gonadal steroids results in brain sexual differentiation. Postnatally, hypothalamic gamma-aminobutyric acid (GABA) levels are almost double in males versus females. We hypothesized that increased GABA neonatally results in masculinization. Males, females, and androgenized females were infused intrahypothalamically with antisense oligonucleotides against glutamic acid decarboxylase (GAD) mRNA at birth to reduce GABA synthesis. GAD protein and GABA levels were reduced 24 hr later without obvious toxic effects, as determined by histological examination. As adults, neonatally antisense-treated, androgenized females showed reduced intromission-like behavior and lordosis quotients compared with vehicle and scrambled controls. Lordosis quotients were reduced about 50% in nonandrogenized females versus vehicle and scrambled controls. These data suggest that GABA is involved in mediating brain sex differentiation and may act in both males and females.

2/3,AB/5 (Item 5 from file: 155)  
DIALOG(R) File 155:MEDLINE(R)

10909231 20452769 PMID: 10996408

Anti-sense oligonucleotides, for progesterin receptors in the VMH and glutamic acid decarboxylase in the VTA, attenuate progesterone-induced lordosis in hamsters and rats.

Frye C A; Murphy R E; Platek S M  
Department of Psychology, The University at Albany-SUNY, 1400 Washington  
Avenue, Albany, NY 12222, USA. cafrye@cnsunix.albany.edu

Behavioural brain research (NETHERLANDS) Oct 2000, 115 (1) p55-64,  
ISSN 0166-4328 Journal Code: 8004872

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Immunocytochemical (ICC) staining for progesterone (P) receptors (PRs)

and glutamic acid decarboxylase (GAD), the enzyme responsible for GABA production, reveal that there are many PRs in the ventral medial hypothalamus (VMH) and many GAD containing neurons in the ventral tegmental area (VTA). To investigate P's action on lordosis in the VMH and VTA, anti-sense oligos specific to PRs and GAD (65&67) were intracerebrally infused into the VMH and VTA of 24 ovariectomized hamsters and 40 ovariectomized rats. Estradiol benzoate (2 microg) primed hamsters and rats were infused to the VMH and the VTA with either PR (250 ng/1.0 microl infusion) or GAD (500 ng/1.0 microl infusion) anti-sense oligos, their scramble controls, or saline vehicle at hour 0 and again at hour 24. At hr 44, rodents were subcutaneously injected with P (500 microg) and were tested for sexual receptivity with a male 4 h later. There were significant reductions in lordosis of hamsters and rats following PR anti-sense infusions to the VMH compared to scrambled or vehicle control infusions. Effects of PR anti-sense to the VMH were not different from combined VMH and VTA PR anti-sense infusions; however, VMH infusions reduced lordosis compared to VTA-only anti-sense infusions. GAD anti-sense infusions reduced lordosis when infused into the VTA, compared to scrambled or saline vehicle infusions. Lordosis responsiveness following VTA GAD anti-sense infusions was not different from combined VMH and VTA infusions, but VTA infusions of GAD anti-sense reduced lordosis compared to VMH-only anti-sense infusions. These data suggest that in the VMH, PRs are important for P-facilitated lordosis, whereas in the VTA, GABAergic neurons may be an important substrate for mediating P's actions on lordosis of rodents.

2/3,AB/6 (Item 6 from file: 155)  
DIALOG(R) File 155:MEDLINE(R)

10888116 20411240 PMID: 10954415

Transient suppression of cortactin ectopically induces large telencephalic neurons towards a GABAergic phenotype.

Cheng Y; Leung S; Mangoura D

Department of Pediatrics, Committee on Neurobiology and Committee on Cell Physiology, Chicago, IL 60637, USA.

Journal of cell science (ENGLAND) Sep 2000, 113 ( Pt 18) p3161-72,  
ISSN 0021-9533 Journal Code: 0052457

Contract/Grant No.: HD-09402; HD; NICHD

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Excitatory and inhibitory neuronal cell fates require specific expression of both neurotransmitter and morphological phenotypes. The role of the F-actin cytoskeleton in morphological phenotypes has been well documented, but its role in neurotransmitter phenotype expression remains unknown. Here we present evidence that the F-actin binding protein cortactin participates in determining both aspects of cell fate in large telencephalic neurons. We show that the expression of cortactin was upregulated early in development just prior to appearance of GABAergic neurons in the chick telencephalon at embryonic day 6. This program was faithfully maintained in primary neuronal cultures derived from E6 telencephalon, where immature neurons differentiate either to large pyramidal and large stellate excitatory neurons or to small inhibitory GABAergic neurons. Immunostaining revealed that cortactin was enriched in areas of membrane budding, growth cones, and in the cell cortex of immature neurons. With differentiation, intense punctate staining was also observed in an extraction-resistant cytosolic compartment of the soma and processes. More importantly, suppression of cortactin by inhibition of cortactin mRNA translation with antisense oligonucleotides caused permanent phenotypic changes. Specifically, a transient suppression of cortactin was achieved in immature neurons with a single exposure to antisense oligonucleotides. This inhibition first induced both the expression of mRNA and the enzymatic activity of GAD

significantly earlier than in control neurons. Second, cortactin-suppressed large projectional neurons exhibited significantly shorter processes and growth cones with protrusive filopodia and an enlarged lamellipodia veil. Most importantly, this remodeling of neuritic outgrowth in projectional somata was accompanied by the ectopic induction of GABA (\*-aminobutyric acid) expression. Considering this data altogether, it appears that cortactin may function to suppress concurrently several parameters of the GABAergic program in large developing neurons.

2/3,AB/7 (Item 7 from file: 155)  
DIALOG(R) File 155:MEDLINE(R)

10755106 20312855 PMID: 10854247

Glutamic acid decarboxylase-expressing astrocytes exhibit enhanced energetic metabolism and increase PC12 cell survival under glucose deprivation.

Bellier J P; Sacchettoni S; Prod'hon C; Perret-Liaudet A; Belin M F; Jacquemont B

Laboratoires de Neuro-Virologie Moleculaire et de Neurobiologie Experimentale et Physiopathologie, INSERM U. 433, France.

Journal of neurochemistry (UNITED STATES) Jul 2000, 75 (1) p56-64,  
ISSN 0022-3042 Journal Code: 2985190R

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Astrocytes play a key role by catabolizing glutamate from extracellular space into glutamine and tricarboxylic acid components. We previously produced an astrocytic cell line that constitutively expressed glutamic acid decarboxylase (GAD67), which converts glutamate into GABA to increase the capacity of astrocytes to metabolize glutamate. In this study, GAD -expressing astrocytes in the presence of glutamate were shown to have increased energy metabolism, as determined by a moderate increase of 3-(4, 5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide reduction, by an increased ATP level, and by enhanced lactate release. These changes were due to GAD transgene expression because transient expression of a GAD antisense plasmid resulted in partial suppression of the ATP level increase. These astrocytes had an increased survival in response to glucose deprivation in the presence of glutamate compared with the parental astrocytes, and they were also able to enhance survival of a neuronal-like cell line (PC12) under glucose deprivation. This protection may be partially due to the increased lactate release by GAD -expressing astrocytes because PC12 cell survival was enhanced by lactate and pyruvate under glucose deprivation. These results suggest that the establishment of GAD expression in astrocytes enhancing glutamate catabolism could be an interesting strategy to increase neuronal survival under hypoglycemia conditions.

2/3,AB/8 (Item 8 from file: 155)  
DIALOG(R) File 155:MEDLINE(R)

10457950 99445766 PMID: 10515993

Evidence that wakefulness and REM sleep are controlled by a GABAergic pontine mechanism.

Xi M C; Morales F R; Chase M H

Department of Physiology and the Brain Research Institute, UCLA School of Medicine, Los Angeles, California 90095, USA.

Journal of neurophysiology (UNITED STATES) Oct 1999, 82 (4) p2015-9,  
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The pontine microinjection of the inhibitory neurotransmitter GABA and its agonist induced prolonged periods of wakefulness in unanesthetized, chronic cats. Conversely, the application of bicuculline, a GABA(A) antagonist, resulted in the occurrence of episodes of rapid eye movement (REM) sleep of long duration. Furthermore, administration of antisense oligonucleotides against glutamic acid decarboxylase (GAD) mRNA into the same area produced a significant decrease in wakefulness and an increase in REM sleep. Microinjections of glycine, another major inhibitory neurotransmitter in the CNS, and its antagonist, strychnine, did not have any effect on the behavioral states of sleep and wakefulness. These data argue forcibly that 1) GABAergic neurons play a pivotal role in determining the occurrence of both wakefulness and REM sleep and 2) the functional sequelae of inhibitory GABA actions within the pontine reticular formation are excitatory directives and/or behaviors.

2/3,AB/9 (Item 9 from file: 155)  
DIALOG(R) File 155:MEDLINE(R)

10410852 99402146 PMID: 10475161

GABA(A), D1, and D5, but not progesterin receptor, antagonist and anti-sense oligonucleotide infusions to the ventral tegmental area of cycling rats and hamsters attenuate lordosis.

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In hamsters, progesterone (P) in the hypothalamus and ventral tegmental area (VTA) is necessary for receptivity; in rats, hypothalamic P induces receptivity and midbrain P further enhances it. How P exerts its effects in the VTA on lordosis is of interest because few estrogen-induced P receptors (PRs) have been identified there. Sexual receptivity of rats and hamsters is enhanced when P's actions in the VTA are restricted to the membrane and when the gamma-aminobutyric acid (GABA)A agonist, muscimol, is infused into the VTA, but attenuated with infusions of the GABA(A) antagonist, bicuculline. The dopamine (DA) agonist, SKF38393, rapidly enhances receptivity when infused intravenously; this effect can be blocked by both DA receptor (DR) and PR antagonists. This study investigated the importance of PRs, glutamic acid decarboxylase (GAD), the enzyme responsible for GABA production, GABA(A) receptors (GBRs), and DRs in the VTA of cycling rats and hamsters for the expression of lordosis. Proestrous and diestrous animals implanted with bilateral VTA cannulae were pre-tested for receptivity, infused with either an antagonist (RU38486 (20 microg), bicuculline (100 ng), SCH23390 (100 ng)), anti-sense oligonucleotide (against PR (250 ng), GAD (500 ng), D1 (500 ng), D5 (250 ng)), or control infusions to each cannulae and re-tested. Vehicle and scrambled oligonucleotides were infused as controls and elicited similar effects. Antagonists of GBRs and DRs significantly reduced lordosis on post-tests compared to the PR antagonist and control conditions in rats and hamsters. Lordosis was significantly reduced, compared to controls, only by anti-sense oligonucleotides for GAD and D1- and D5-DR subtypes. These data suggest that in the VTA GABAergic and dopaminergic neurons may be more important in the mediation of sexual receptivity than neurons containing intracellular PRs.

2/3,AB/10 (Item 10 from file: 155)  
DIALOG(R) File 155:MEDLINE(R)

10359746 99337804 PMID: 10407193

Deafferentation induced changes in GAD67 and GluR2 mRNA expression in mouse somatosensory cortex.

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Partial vibrissotomy in adult mice induces body map plasticity in SI barrel cortex. To examine if the disturbed balance of cortical activation affects the excitatory and inhibitory neurotransmitter systems, we studied glutamic acid decarboxylase (GAD 67) and AMPA receptor subunit GluR2 mRNA expression in the barrel cortex. At varying times post-vibrissotomy, sparing row C of whiskers on one side of the snout, the brains were processed for in situ hybridization using specific [(35)S]oligonucleotides to detect the laminar localization of GAD67 and GluR2 mRNAs. Three and seven days after vibrissotomy, the expression of GAD67 was decreased in the deafferented cortex, while 30 days post-lesion, no effects were observed. At 3 days post-lesion, an ipsilateral decrease in GAD67 mRNA expression was also observed. No decreases in GluR2 transcripts were found in the deafferented cortex, but an increased expression was observed in the representation of the spared row C of whiskers 3 days after vibrissotomy. Seven and 30 days post lesion no changes in GluR2 expression were found. These data indicate that in the barrel cortex, peripheral deafferentation transiently regulates GAD67 and GluR2 expression at the transcriptional level. We suggest that this may be a manifestation of adaptive processes. Copyright 1999 Elsevier Science B.V.

2/3,AB/11 (Item 11 from file: 155)  
DIALOG(R) File 155:MEDLINE(R)

10276915 99263142 PMID: 10325232

Control of autoimmune diabetes in NOD mice by GAD expression or suppression in beta cells.

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Science (UNITED STATES) May 14 1999, 284 (5417) p1183-7, ISSN 0036-8075 Journal Code: 0404511

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Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Glutamic acid decarboxylase (GAD) is a pancreatic beta cell autoantigen in humans and nonobese diabetic (NOD) mice. beta Cell-specific suppression of GAD expression in two lines of antisense GAD transgenic NOD mice prevented autoimmune diabetes, whereas persistent GAD expression in the beta cells in the other four lines of antisense GAD transgenic NOD mice resulted in diabetes, similar to that seen in transgene-negative NOD mice. Complete suppression of beta cell GAD expression blocked the generation of diabetogenic T

cells and protected islet grafts from autoimmune injury. Thus, beta cell-specific **GAD** expression is required for the development of autoimmune diabetes in NOD mice, and modulation of **GAD** might, therefore, have therapeutic value in type 1 diabetes.

2/3,AB/12 (Item 12 from file: 155)  
DIALOG(R) File 155:MEDLINE(R)

10276905 99288683 PMID: 10366347  
**GAD**, a single autoantigen for diabetes.  
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Science (UNITED STATES) May 14 1999, 284 (5417) p1135, 1137, ISSN  
0036-8075 Journal Code: 0404511  
Comment on Science. 1999 May 14;284(5417) 1183-7; Comment on PMID  
10325232  
Document type: Comment; Journal Article  
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2/3,AB/13 (Item 13 from file: 155)  
DIALOG(R) File 155:MEDLINE(R)

10255075 99237792 PMID: 10223281  
An increase in glutamate release follows a decrease in gamma aminobutyric acid and the pubertal increase in luteinizing hormone releasing hormone release in the female rhesus monkeys.  
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Journal of neuroendocrinology (ENGLAND) Apr 1999, 11 (4) p275-82, ISSN 0953-8194 Journal Code: 8913461  
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Previously we have shown that release of gamma-aminobutyric acid (GABA) in the stalk-median eminence (S-ME) is high in prepubertal monkeys and that a decrease in GABA release triggers the onset of puberty. However, it is still unclear how disinhibition of the luteinizing hormone releasing hormone (LHRH) neuronal system from GABA input is followed (or accompanied) by an increase in stimulatory signals, such as glutamatergic input to LHRH neurons. To clarify the temporal relationship between the reduction of the GABAergic inhibitory signal and the enhancement of the glutamatergic stimulatory signal in the control of LHRH release at the onset of puberty, we conducted two experiments using a push-pull perfusion method. In the first experiment, we measured developmental changes in release of LHRH, GABA, and glutamate in the S-ME. LHRH levels were very low in prepubertal monkeys, increased to higher levels in early pubertal monkeys, with the highest LHRH levels occurring in mid-pubertal monkeys. As we previously observed, GABA levels were high in prepubertal monkeys and then decreased in early- and mid-pubertal monkeys. In contrast, glutamate levels were very low in prepubertal monkeys, increased dramatically in early pubertal monkeys, and then slightly decreased in mid-pubertal monkeys, although mid-pubertal levels remained much higher than prepubertal levels. In the second experiment, we measured GABA, glutamate and LHRH in the same samples obtained from prepubertal monkeys which were infused with an **antisense** oligodeoxynucleotide (AS) for glutamic acid decarboxylase (**GAD**) 67 mRNA into the S-ME. GAD67 is a catalytic enzyme for GABA

synthesis from glutamate, and AS GAD67 mRNA interferes with GAD67 synthesis. Infusion of the AS GAD67 induced a decrease in GABA release, which subsequently resulted in an increase in LHRH release. Surprisingly, glutamate release also increased several hours after the decrease in GABA release, and the increased LHRH release continued. These data are interpreted to mean that a decrease in GABA synthesis by interference with GAD67 synthesis and the reduction of GABA release in the S-ME trigger an increase in LHRH release, but that a subsequent increase in glutamate release in the S-ME further contributes to the pubertal increase in LHRH release at the onset of puberty. The data further support our hypothesis that GAD plays an important role in the mechanism of the onset of puberty.

2/3,AB/14 (Item 14 from file: 155)  
DIALOG(R)File 155:MEDLINE(R)

10133092 99124487 PMID: 9927297

A role of gamma-amino butyric acid (GABA) and glutamate in control of puberty in female rhesus monkeys: effect of an **antisense** oligodeoxynucleotide for GAD67 messenger ribonucleic acid and MK801 on luteinizing hormone-releasing hormone release.

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Endocrinology (UNITED STATES) Feb 1999, 140 (2) p705-12, ISSN 0013-7227 Journal Code: 0375040

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Languages: ENGLISH

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Record type: Completed

Previously we have shown that gamma-aminobutyric acid (GABA) is an inhibitory neurotransmitter restricting the pubertal increase in LHRH release in juvenile monkeys, and that interfering with GABA synthesis with an **antisense** oligodeoxynucleotide (AS) for glutamic acid decarboxylase (GAD67) mRNA results in an increase in LHRH release in prepubertal monkeys. GAD67 is a catalytic enzyme that synthesizes GABA from glutamate. To further clarify the role of GABA in puberty, we examined whether the inhibition of LHRH release by GABA continues after the onset of puberty and whether input from glutamatergic neurons plays any role in the onset of puberty when GABA inhibition declines, using a push-pull perfusion method. In Study I, the effects of the AS GAD67 mRNA on LHRH release in pubertal monkeys (34.3 +/- 1.5 months of age, n = 8) were examined, and the results were compared with those in prepubertal monkeys (18.5 +/- 0.4 months, n = 12). Direct infusion of AS GAD67 (1 microM) into the stalk-median eminence (S-ME) for 5 h stimulated LHRH release in both prepubertal and pubertal monkeys. However, the increase in LHRH release in pubertal monkeys was significantly (P < 0.01) smaller than that in prepubertal monkeys. Infusion of a scrambled oligo as a control was without effect in either group. In Study II, to examine the possibility that an increase in glutamate tone after the reduction of an inhibitory GABA tone contributes to the AS GAD67-induced LHRH increase, the effects of the NMDA receptor blocker MK801 (5 microM) on LHRH release were tested in monkeys treated with AS GAD67. MK801 infusion into the S-ME during the treatment of AS GAD67 (1 microM) suppressed the AS GAD67-induced LHRH release in both age groups. MK801 alone did not cause any significant effect in either group. The data are interpreted to mean that GABA continues to suppress LHRH release after the onset of puberty, although the degree of suppression is weakened considerably after the onset of puberty, and that the increased LHRH release after AS GAD67 treatment may be partly due to an increase in glutamate tone mediated by NMDA receptors, as well as due to the decrease in GABA release following the decrease in GAD synthesis. Taken